Epigenetic gene regulation during the differentiation of human embryonic stem cells: Impact on neural repair

Grant Award Details

Epigenetic gene regulation during the differentiation of human embryonic stem cells: Impact on neural repair

Grant Type: Comprehensive Grant

Grant Number: RC1-00111

Investigator:

Name:	Guoping Fan
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Neurological Disorders, Stroke

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: $2,412,995

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Grant Application Details

Application Title:	Epigenetic gene regulation during the differentiation of human embryonic stem cells: Impact on neural repair
Public Abstract:	Human embryonic stem cells (hESCs) have the potential to become all sorts of cells in human body including nerve cells. Moreover, hESCs can be expanded in culture plates into a large quantity, thus serving as an ideal source for cell transplantation in clinical use. However, the existing hESC lines are not fully characterized in terms of their potential to become specific cell types such as nerve cells. It is also unclear if the nerve cells that are derived from hESCs are totally normal when tested in cell transplantation experiments. One of the goals for our proposal is to compare the quality and the potential of eight lines of hESCs in their capacity to become nerve cells. To measure if the nerve cells that are derived from hESCs are normal when compared to the nerve cells in normal human beings, we will examine the levels of gene expression and the mechanisms that control gene expression in hESC-derived nerve cells. Specifically, we will examine the pattern of DNA modification, namely DNA methylation, in the DNA of nerve cells. This DNA modification is involved in the inhibition of gene expression. It is known that if DNA methylation pattern is abnormal, it can lead to human diseases including cancer and mental retardation disorders. We will use a DNA microarray technology to identify DNA methylation pattern in the critical regions where gene expression is controlled. Our recent results suggest that increased DNA methylation is observed in hESC-derived nerve cells. In this proposal, we will also test if we can balance the level of DNA methylation through pharmacological treatment of enzymes that are responsible for DNA methylation. Finally, we will test if hESC-derived nerve cells can repair the brain after injury . A mouse stroke model will be used for testing the mechanisms stem cell-mediated repair and recovery in the injured brain and for selecting the best nerve cells for cell transplantation. Our study will pave the way for the future use of hESC-derived nerve cells in clinical treatment of nerve injury and neurodegenerative diseases such as stroke and Parkinson's disease.
Statement of Benefit to California:	Neurodegenerative diseases such as stroke are the leading cause of adult disability. Stroke produces an area of damage in the brain which frequently causes the loss of crucial brain functions such as sensory and movement control, language skills, and cognition capability. Stem cell transplantation has emerged as a method that may improve recovery in these brain areas. Studies of stem cell transplantation after stroke have been limited because many of the transplanted cells do not survive, the appropriate regions for transplantation have not been identified, and the mechanisms by which transplanted stem cells improve recovery have not been determined. Also, there have been no studies of human embryonic stem cell transplantation after stroke. For the use of stem cell therapy in stroke patients, human embryonic stem cell lines have to be grown and tested for their efficacy in repairing the brain after stroke. We have recently found that the process of growing human embryonic stem cells in culture introduces genetic modifications in some of these cell lines that may decrease survival of the cells in the brain and impair their ability to repair the injured brain. The experiments in this grant will determine which human embryonic stem cell lines do not undergo this negative genetic modification. The optimum human embryonic stem cell lines will then be systematically tested for the location in the stroke brain that produces survival and integration, and the mechanisms of repair that these cells mediate in the brain after stroke. These studies will specifically test the role of human embryonic stem cells in improving sensory and movement functions after stroke. In summary, these studies will establish protocols for the proper growth of human embryonic stem cell lines, the lines that are most effective for repairing the brain after stroke, and the principles behind how human embryonic stem cells repair the brain. These results are applicable to other kinds of neurodegenerative conditions, such as Parkinsons, Alzheimer's and Huntington's diseases, and to the growth and culture of human embryonic stem cells in general for repair of disease of other human tissues.